PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

To:

CONNELL, Gary, J.
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ETATS-UNIS D'AMERIQUE

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

Date of mailing *(day/month/year)* 04 February 2010 (04.02.2010)	
Applicant's or agent's file reference 5941-65-PUS-CIP-PCT	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2008/070930	23 July 2008 (23.07.2008)	23 July 2007 (23.07.2007)

Applicant
THE REGENTS OF THE UNIVERSITY OF COLORADO et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 5941-65-PUS-CIP-PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2008/070930	International filing date *(day/month/year)* 23 July 2008 (23.07.2008)	Priority date *(day/month/year)* 23 July 2007 (23.07.2007)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant THE REGENTS OF THE UNIVERSITY OF COLORADO		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 26 January 2010 (26.01.2010)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yolaine Cussac e-mail: pt05.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
GARY J. CONNELL
SHERIDAN ROSS P.C.
1560 BROADWAY, SUITE 1200
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	06 FEB 2009
Applicant's or agent's file reference 5941-65-PUS-CIP-PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 08/70930	23 July 2008 (23.07.2008)	23 July 2007 (23.07.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68, C40B 30/04, A61P 35/00 (2008.04)
USPC - 435/6, 435/7.23, 506/9

Applicant THE REGENTS OF THE UNIVERSITY OF COLORADO

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	31December 2008 (31.12.2008)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/70930

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☒ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☒ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/70930

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 13-22 and 35-39

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 13-22 and 35-39 are so unclear that no meaningful opinion could be formed *(specify)*:
Claims 13-22 and 35-39, because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 13-22 and 35-39

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Invention 1: claims 1, 2, 8-12, 23-24, 30-34, 40-42, 48-49, 55-65, 70, 75-76 and 81-82, limited to the gene E-cadherin and SEQ ID NO: 3. Please note that there is an un-numbered claim between claims 70 and 71. This un-numbered claim also falls under the grouping of Invention 1.

Invention 2: claims 1, 3, 8-12, 23, 25, 30-34, 40-41, 45, 48, 50, 55-64, 66, 70, 71 , 75, 77, 81 and 83, limited to the gene RAB25 and SEQ ID NO: 83.

Invention 3: claims 1, 4, 8-12, 23, 26, 30-34, 40-41, 46, 48, 51, 55-64, 67, 70, 72 , 75, 78, 81 and 84, limited to the gene integrin beta 6 (ITGB6) and SEQ ID NO: 137.

Invention 4: claims 1, 4, 8-12, 23, 26, 30-34, 40-41, 46, 48, 51, 55-64, 68, 70, 73 , 75, 79, 81 and 85, limited to the gene integrin beta 6 (ITGB6) and SEQ ID NO:52.

Invention 5: claims 1, 5, 8-12, 23, 27, 30-34, 40-41, 47-48, 52, 55-64, 69, 70, 74-75, 80-81 and 86, limited to the gene vimentin and SEQ ID NO: 195.

Invention 6: claims 1, 6, 8-12, 23, 28, 30-34, 40-41, 43, 48, 53, 55-64, 70, 75, 81 and 87, limited to the gene ZEB1 and SEQ ID NO: 196.

Invention 7: claims 1, 7-12, 23, 29-34, 40-41, 44, 48, 54-64, 70, 75, 81 and 88, limited to the gene SIP1 and SEQ ID NO: 197.

The inventions listed as Inventions 1-7 do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule13.2 they lack the same or corresponding special technical feature. According to PCT Rule 13.2, unity of invention exists only when the same or corresponding technical feature is shared by all claimed inventions.

The feature common to all of the claims is the detection of genes whose expression is correlated with sensitivity to an antibody that binds to EGFR. However, this common feature is known in the art and cannot serve as the special technical feature. The article entitled 'Biomarkers for prediction of sensitivity to EGFR inhibitors in non-small cell lung cancer' by Hirsch et al. (Hirsch et al., Biomarkers for prediction of sensitivity to EGFR inhibitors in non-small cell lung cancer, Current Opinion in Oncology, March 2005, Vol 17, No 2, pp 118-122) discloses the detection of genes whose expression is correlated with sensitivity to an antibody that binds to EGFR (p 118, abstract; p 121, Table 1). Thus, the claimed inventions do not share the same or corresponding special technical feature, and unity of invention is lacking.

In this case, the first named Invention and first named species that will be searched without additional fees is Invention 1 represented by claims 1, 2, 8-12, 23-24, 30-34, 40-42, 48-49, 55-63, 64a, 64b, 65a, 65b, 70, 75-76 and 81-82, limited to the gene E-cadherin and SEQ ID NO: 3.

In order for more than the above inventions to be examined, the appropriate additional examination fees must be paid and the desired species clearly identified.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. 1-2, 8-12, 23-24, 30-34, 40-42, 48-49, 55-63, 64a/b, 65a/b, 70, 75-76 and 81-82, 89

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/70930

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	10-12,32-34,55-60, 63,64a/b,65a/b,70,75-76,81-82,89	YES
	Claims	1,2, 8-9, 23-24, 30-31, 40-42, 48-49, 61-62	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-2, 8-12, 23-24, 30-34 (see continuation below)	NO
Industrial applicability (IA)	Claims	1, 2, 8-12, 23-24, 30-34 (see continuation below)	YES
	Claims	none	NO

2. Citations and explanations:
Continuation of Box No. V.1:

Inventive step (IS)
NO – 40-42, 48-49, 55-63, 64a, 64b, 65a, 65b, 70, 75, 89

Industrial applicability (IA)
YES -- 40-42, 48-49, 55-63, 64a, 64b, 65a, 65b, 70, 75, 89

Claims 1, 2, 8, 9, 23, 24, 30, 31, 40-42, 48, 49, 61, 62 lack novelty under PCT Article 33(2) as being anticipated by US.2006/0211060 A1 to Haley et al. (hereinafter 'Haley').

Regarding claim 1, Haley discloses a diagnostic method, comprising:
a) providing a sample of cancer cells of epithelial origin from a patient to be tested (para [0020] - 'measuring the level of a candidate epithelial biomarker in neoplastic cell-containing samples from patients with a neoplastic condition');
b) detecting in the sample the expression of at least one gene chosen from a panel of genes whose expression has been correlated with sensitivity or resistance to an antibody that binds EGFR, wherein the gene is E-cadherin (para [0016] - 'assessing the level of an epithelial biomarker expressed by a tumor cell; and predicting the sensitivity of tumor cell growth to inhibition by an EGFR kinase inhibitor, wherein high expression levels of tumor cell epithelial biomarkers correlate with high sensitivity to inhibition by EGFR kinase inhibitors'; para [0190] - 'Suitable monoclonal antibody EGFR kinase inhibitors include, but are not limited to, IMC-C225 (also known as cetuximab or ERBITUX.TM.; Imclone Systems)'; para [0025] - 'NSCLC lines sensitive to EGF receptor inhibition express elevated levels of E-cadherin'); and
c) comparing the level of expression of at least one gene detected in the patient sample to a level of expression of at least one gene that has been correlated with sensitivity or resistance to the antibody that binds EGFR (para [0039] - 'compare E-cadherin levels between sensitive and relatively insensitive tumor cells in FIGS. 2B, 3 and 5').

Regarding claim 2, Haley further discloses detecting expression of E-cadherin (para[0039] - 'compare E-cadherin levels between sensitive and relatively insensitive tumor cells in FIGS. 2B, 3 and 5').

Regarding claim 8, Haley further discloses wherein the antibody is cetuximab (para [0190]).

Regarding claim 9, Haley further discloses wherein the antibody is cetuximab (para [0190]).

Regarding claim 23, Haley discloses a method of detecting sensitivity of an epithelial-origin cancer to an antibody the binds EGFR comprising:
a) detecting in a sample of tumor cells from a patient to be tested, the expression of E-cadherin (para [0020] - 'measuring the level of a candidate epithelial biomarker in neoplastic cell-containing samples from patients with a neoplastic condition'; para [0025] - 'NSCLC lines sensitive to EGF receptor inhibition express elevated levels of E-cadherin');
b) comparing the level of expression of the one or more genes detected in the patient sample to a gene expression level of E-cadherin that has been correlated with sensitivity or resistance to an antibody that binds EGFR (para[0039] - 'compare E-cadherin levels between sensitive and relatively insensitive tumor cells in FIGS. 2B, 3 and 5'; para [0016] - 'assessing the level of an epithelial biomarker expressed by a tumor cell; and predicting the sensitivity of tumor cell growth to inhibition by an EGFR kinase inhibitor, wherein high expression levels of tumor cell epithelial biomarkers correlate with high sensitivity to inhibition by EGFR kinase inhibitors '); and
c) identifying the expression level of the one or more genes detected in the patient sample that are statistically more similar to the expression level of E-cadherin that has been correlated with sensitivity than to the the expression levels that have been correlated with resistance (para [0016] - 'assessing the level of an epithelial biomarker expressed by a tumor cell; and predicting the sensitivity of tumor cell growth to inhibition by an EGFR kinase inhibitor, wherein high expression levels of tumor cell epithelial biomarkers correlate with high sensitivity to inhibition by EGFR kinase inhibitors'; para [0190] - 'Suitable monoclonal antibody EGFR kinase inhibitors include, but are not limited to, IMC-C225 (also known as cetuximab or ERBITUX.TM.; Imclone Systems)'; para [0025] - 'NSCLC lines sensitive to EGF receptor inhibition express elevated levels of E-cadherin').

--Please See Continuation Sheet--

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

There is an un-numbered claim between claims 70 and 71. For the purpose of this opinion, the un-numbered claim has been designated "claim 89".

The claim 60 shoud be The method of claim 55, wherein the EGFR inhibitor is semaxinib instead of The method of claim 55, wherein the EGFR inhibitor is semazinib.

The claim numbers 64-65 have been duplicated. For the purpose of this opinion, the first set have been designated as claims 64a and 65a, and the second set as claims 64b and 65b.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box No. V(2) -- citations and explanations

Regarding claim 24, Haley further discloses wherein the gene is E-cadherin (para[0039]).

Regarding claim 30, Haley further discloses wherein the antibody is cetuximab (para [0190]).

Regarding claim 31, Haley further discloses wherein the antibody is cetuximab (para [0190]).

Regarding claim 40, Haley discloses a kit comprising reagents for the detection of expression levels that have been correlated with sensitivity or resistance to an EGFR inhibitor of E-cadherin (para [0133] - 'kits for detecting the presence of a biomarker protein or nucleic acid in a biological sample. Such kits can be used to determine if a subject is less susceptible to inhibition by EGFR kinase inhibitors. For example, the kit can comprise a labeled compound or agent capable of detecting a biomarker protein or nucleic acid in a biological sample and means for determining the amount of the protein or mRNA in the sample'; para[0039] - 'compare E-cadherin levels between sensitive and relatively insensitive tumor cells in FIGS. 2B, 3 and 5').

Regarding claim 41, Haley further discloses the kit further comprsing a compilation comprising E-cadherin expression levels that have been correlated with sensitivity or resistance to an EGFR inhibitor (para [0016] - 'assessing the level of an epithelial biomarker expressed by a tumor cell; and predicting the sensitivity of tumor cell growth to inhibition by an EGFR kinase inhibitor, wherein high expression levels of tumor cell epithelial biomarkers correlate with high sensitivity to inhibition by EGFR kinase inhibitors'; para [0025] - 'NSCLC lines sensitive to EGF receptor inhibition express elevated levels of E-cadherin').

Regarding claim 42, Haley further discloses wherein the gene is E-cadherin (para[0039]).

Regarding claim 48, Haley discloses a method of treating cancer in a patient (para [0018]), comprising:
a) detecting the expression levels of E-cadherin (para [0025] - 'NSCLC lines sensitive to EGF receptor inhibition express elevated levels of E-cadherin'); and
b) administering an EGFR inhibitor (para [0018] - 'administering to said patient a therapeutically effective amount of an EGFR kinase inhibitor').

Regarding claim 49, Haley further discloses wherein the gene is E-cadherin (para[0039]).

Regarding claim 61, Haley further discloses wherein the EGFR inhibitor is cetuximab (para [0190]).

Regarding claim 62, Haley further discloses wherein the EGFR inhibitor is cetuximab (para [0190]).

Claims 10, 12, 32, 34, 55-60, 63, 65a lack an inventive step under PCT Article 33(3) as being obvious over Haley in view of US 2007/0020261 A1 to Sliwkowski et al. (hereinafter 'Sliwkowski').

Regarding claim 10, Haley discloses the method of claim 8, but does not specifically disclose that the antibody is panitumumab. However, Sliwkowski discloses a treatment of tumor comprising administering to a human subject with an EGFR inhibitor wherein the antibody is panitumumab (para [0087] - 'human antibodies that bind EGFR, such as ABX-EGF or Panitumumab'). It would have been obvious to one of ordinary skill in the art to combine Haley and Sliwkowski in order to develop the method as set forth in the claim 10 because Sliwkowski suggests that panitumumab was well known in the art as an EGFR antibody (Sliwkowski para [0087]).

Regarding claim 12, Sliwkowski further discloses wherein the antibody is matuzumab (para [0087] - 'EMD7200 (matuzumab) a humanized EGFR antibody directed against EGFR').

Regarding claim 32, Haley teaches the method of claim 30, but does not specifically disclose that the antibody is panitumumab. However, Sliwkowski discloses a treatment of tumor comprising administering to a human subject with an EGFR inhibitor, wherein the antibody is panitumumab (para [0087] - 'human antibodies that bind EGFR, such as ABX-EGF or Panitumumab'). It would have been obvious to one of ordinary skill in the art to combine Haley and Sliwkowski in order to develop the method as set forth in the claim 32 because Sliwkowski suggests that panitumumab was well known in the art as an EGFR antibody (Sliwkowski para [0087]).

Regarding claim 34, Sliwkowski further discloses wherein the antibody is matuzumab (para [0087]).

Regarding claim 55, Haley discloses the method of claim 48, but does not specifically disclose that the EGFR inhibitor is gefitinib. However, Sliwkowski discloses a treatment of tumor comprising administering to a human subject with an EGFR inhibitor wherein the EGFR inhibitor is gefitinib (para[0087] - 'EGFR antagonists gefitinib'). It would have been obvious to one of ordinary skill in the art to combine Haley and Sliwkowski in order to develop the method as set forth in the claim 55 because Sliwkowski suggests that gefitinib was well known in the art as an EGFR antibody (Sliwkowski para [0087]).

Regarding claim 56, Sliwkowski further discloses wherein the EGFR inhibitor is gefitinib (para[0087] - 'EGFR antagonists gefitinib').

Regarding claim 57, Sliwkowski further discloses wherein the EGFR inhibitor is erlotinib (para [0044] - 'In yet another specific embodiment, the EGFR inhibitor erlotinib').

Regarding claim 58, Sliwkowski further discloses wherein the EGFR inhibitor is imatinib (para [0201] - 'inhibitors such as Imatinib').

--Please See Continuation Sheet--

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US 08/70930

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box No. V(2) – citations and explanations

Regarding claim 59, Sliwkowski further discloses wherein the EGFR inhibitor is lapatinib (para [0084] - 'HER2 and EGFR dual tyrosine kinase inhibitors such as lapatinib').

Regarding claim 60, Sliwkowski further discloses wherein the EGFR inhibitor is semaxinib (para [0201] - 'inhibitors include the EGFR-targeted drugs Semaxinib (Sugen)').

Regarding claim 63, Sliwkowski further discloses wherein the EGFR inhibitor is panitumumab (para [0087] - 'human antibodies that bind EGFR, such as ABX-EGF or Panitumumab').

Regarding claim 65a, Sliwkowski further discloses wherein the EGFR inhibitor is metuzumab (para [0087] - 'EMD7200 (matuzumab) a humanized EGFR antibody directed against EGFR').

Claims 11, 33, 64a lack an inventive step under PCT Article 33(3) as being obvious over Haley in view of the article entitled "Nimotuzumab: Evidence of Clinical Benefit Without Rash" by Allan (hereinafter 'Allan').

Regarding claim 11, Haley discloses the method of claim 8, but does not specifically disclose that the antibody is nimotuzumab. However, Allan discloses the epidermal growth factor receptor (EGFR) targeting monoclonal antibody nimotuzumab (pg 760, col 1, para 1). It would have been obvious to one of ordinary skill in the art to combine Haley and Allan in order to develop the method as set forth in the claim 11 because Allan suggests that nimotuzumab was well known in the art as an EGFR antibody (Allan pg 760, col 1, para 1).

Regarding claim 33, Haley discloses the method of claim 30, but does not specifically disclose wherein the antibody is nimotuzumab. However, Allan discloses the epidermal growth factor receptor (EGFR) targeting monoclonal antibody nimotuzumab (pg 760, col 1, para 1). It would have been obvious to one of ordinary skill in the art to combine Haley and Allan in order to develop the method as set forth in the claim 33 because Allan suggests that nimotuzumab was well known in the art as an EGFR antibody (Allan pg 760, col 1, para 1).

Regarding claim 64a, Haley discloses the method of claim 61, but does not specifically disclose that the EGFR inhibitor is nimotuzumab. However, Allan discloses the epidermal growth factor receptor (EGFR) targeting monoclonal antibody nimotuzumab (pg 760, col 1, para 1). It would have been obvious to one of ordinary skill in the art to combine Haley and Allan in order to develop the method as set forth in the claim 64 because Allan suggests that nimotuzumab was well known in the art as an EGFR antibody (Allan pg 760, col 1, para 1).

Claims 64b, 65b, 70, 75, 76, 81, 82, 89 lack an inventive step under PCT Article 33(3) as being obvious over Haley in view of US 2002/0045591 A1 to Geiger et al. (hereinafter 'Geiger ').

Regarding claim 64b, Haley discloses the method of claim 1, but does not specifically disclose wherein the one or more genes is of E-cadherin (SEQ ID NO: 3). However, Geiger discloses methods and therapeutic compositions for the treatment of cancer wherein the one or more genes is of E-cadherin (SEQ ID NO: 3) (para [0101] - 'a polynucleotide which comprises a nucleotide sequence encoding a cytoplasmic portion of cadherin. Preferably, the nucleotide sequence includes SEQ ID NO: 47'; SEQ ID NO: 47, which exhibits 100% homology to SEQ ID NO: 3). It would have been obvious to one of ordinary skill in the art to combine Haley and Geiger in order to develop the method as set forth in the claim 64b because Haley teaches a method employing a E-cadherin gene and Geiger teaches a sequence for a E-cadherin gene (Geiger para [0101]).

Regarding claim 65b, Geiger further discloses detecting the expression of E-cadherin (SEQ ID NO: 3) (para [0101]; SEQ ID NO: 47, which exhibits 100% homology to SEQ ID NO: 3).

Regarding claim 70, Haley discloses the method of claim 23, but does not specifically disclose wherein the one or more genes is of E-cadherin (SEQ ID NO: 3). However, Geiger discloses methods and therapeutic compositions for the treatment of cancer wherein the one or more genes is of E-cadherin (SEQ ID NO: 3) (para [0101] - 'a polynucleotide which comprises a nucleotide sequence encoding a cytoplasmic portion of cadherin. Preferably, the nucleotide sequence includes SEQ ID NO: 47'; SEQ ID NO: 47, which exhibits 100% homology to SEQ ID NO: 3). It would have been obvious to one of ordinary skill in the art to combine Haley and Geiger in order to develop the method as set forth in the claim 70 because Haley teaches a method employing a E-cadherin gene and Geiger teaches a sequence for a E-cadherin gene (Geiger para [0101]).

Regarding claim 75, Haley the kit of claim 40, but does not specifically disclose that the one or more genes is of E-cadherin (SEQ ID NO: 3). However, Geiger discloses methods and therapeutic compositions for the treatment of cancer wherein the one or more genes is of E-cadherin (SEQ ID NO: 3) (para [0101] - 'a polynucleotide which comprises a nucleotide sequence encoding a cytoplasmic portion of cadherin. Preferably, the nucleotide sequence includes SEQ ID NO: 47'; SEQ ID NO: 47, which exhibits 100% homology to SEQ ID NO: 3). It would have been obvious to one of ordinary skill in the art to combine Haley and Geiger in order to develop the method as set forth in the claim 75 because Haley teaches a method employing a E-cadherin gene and Geiger teaches a sequence for a E-cadherin gene (Geiger para [0101]).

Regarding claim 76, Geiger further discloses wherein the gene is E-cadherin (SEQ ID NO: 3) (para [0101] - 'a polynucleotide which comprises a nucleotide sequence encoding a cytoplasmic portion of cadherin. Preferably, the nucleotide sequence includes SEQ ID NO: 47'; SEQ ID NO: 47, which exhibits 100% homology to SEQ ID NO: 3).

--Please See Continuation Sheet--

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/70930

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box No. V(2) – citations and explanations

Regarding claim 81, Haleydoes not specifically disclose that the one or more genes is of E-cadherin (SEQ ID NO: 3). However, Geiger discloses Methods and therapeutic compositions for the treatment of cancer wherin the one or more genes is of E-cadherin (SEQ ID NO: 3) (para [0101],a polynucleotide which comprises a nucleotide sequence encoding a cytoplasmic portion of cadherin. Preferably, the nucleotide sequence includes SEQ ID NO: 47.). It would have been obvious to one of ordinary skill in the art to combine Haleydoes and Geiger in order to develop the method as set forth in the claim 81 because E-cadherin (SEQ ID NO: 3) was well known in the art (para [0101]).

Regarding claim 82, Geiger further discloses that the gene is E-cadherin (SEQ ID NO: 3) (para [0101],a polynucleotide which comprises a nucleotide sequence encoding a cytoplasmic portion of cadherin. Preferably, the nucleotide sequence includes SEQ ID NO: 47.).

Regarding claim 89, Geiger further discloses detecting the expression of E-cadherin (para [0101] - 'a polynucleotide which comprises a nucleotide sequence encoding a cytoplasmic portion of cadherin. Preferably, the nucleotide sequence includes SEQ ID NO: 47'; SEQ ID NO: 47, which exhibits 100% homology to SEQ ID NO: 3).

Claims 1, 2, 8-12, 23-24, 30-34, 40-42, 48-49, 55-65, 70, 75-76 and 81-82, 89 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.